



P I / 18

## Umbilical cord stem cell-derived exosomes have neuroprotective potential in a model of preterm white matter injury

**Author:** 1,2) Thomi G., 1) Joerger-Messerli M.S., 1) Haesler V., 1) Schoeberlein A., 1) Surbek D.

**Clinic:** 1) Obstetrics and Gynecology, Inselspital, Bern University Hospital and Department for BioMedical Research (DBMR), 2) Graduate School for Cellular and Biomedical Sciences (GCB)/ 1,2 University of Bern

**Objective:** Survivors of preterm birth are at risk to suffer from white matter injury (WMI) leading to subsequent neurodevelopmental deficits. Preterm-specific WMI is characterized by a disruption of normal developmental myelination of the brain. In animal models of WMI, Wharton's jelly mesenchymal stem/stromal cells (WJ-MSC) derived from umbilical cords restore normal myelination, in part through the release of cell-derived extracellular vesicles like exosomes. We aimed to test the therapeutic potential of WJ-MSC-derived exosomes in an animal model of preterm WMI.

**Study Design:** We isolated exosomes from WJ-MSC culture supernatants using serial centrifugation. Consistent with the etiology of WMI in preterm infants, we introduced brain injury in 3-day old rat pups with lipopolysaccharide i.p. and unilateral carotid artery cauterization followed by hypoxia (8% O<sub>2</sub>). As a treatment, animals received an intranasal administration of infrared-labeled exosomes which were traced inside the bodies of the animals. In a short-term experiment, we analyzed cortical apoptosis and myelination using TUNEL-assay, real-time RT-PCR and Western blot. In a long-time experiment, we tracked the survival and learning capacity of the animals using the Morris water maze assay.

**Results:** Intranasally administered exosomes rapidly translocated to the brain and arrived within 30 min after administration. Treated animals exhibited reduced cortical apoptosis and diminished hypomyelination 9 days after brain injury as the exosomes rescued the loss of myelin basic protein ( $p < 0.05$ ). Exosome treatment doubled the animal's overall survival rate ( $p < 0.01$ ) and improved their learning capacity ( $p < 0.05$ ) 1 month after WMI.

**Conclusion:** Treatment with WJ-MSC-derived exosomes improves survival, partially restores normal developmental myelination and alleviates associated neurodevelopmental deficits. Intranasal administration of WJ-MSC-derived exosomes represents a minimally-invasive and effective treatment for WMI.